Al-Azhar International Medical Journal

Volume 5 | Issue 6 Article 42

7-1-2024

Section: Obstetrics and Gynecology

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How to Cite This Article

Elboghdady, Adel Aly; Mohamed, Mohamed Ibrahim; and Ahmad, Yahia Yahia Mohamed (2024) "Role of Anticoagulant Therapy in Pregnant Women with Antiphospholipid Antibody Syndrome," *Al-Azhar International Medical Journal*: Vol. 5: Iss. 6, Article 42.
DOI: https://doi.org/10.58675/2682-339X.2502

ORIGINAL ARTICLE

Role of Anticoagulant Therapy in Pregnant Women with Antiphospholipid Antibody Syndrome

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Abstract

Background: ***When there is at least one kind of circulating antiphospholipid antibody (aPL), the patient may experience pregnancy morbidity, arterial or venous thrombotic events, and an autoimmune condition known as antiphospholipid syndrome (APS).***

Aim and objectives: ***To detect the role of the administration of anticoagulant drugs in women with APS in improving pregnancy outcomes and its effect on the rate of live births.***

Patient and methods: ***Our study was a prospective randomized control trial. carried out on 80 pregnant ladies and attended El Hussin Hospital Department of Gynecology & obstetrics of Al Azhar University Hospitals with lupus anticoagulant and anticardiolipin immunoglobulin antibody testing consistently positive from January 2022 - January 2022.***

Results: ***There was a significant difference between the two studied groups as regards miscarriages, EGA at loss, live birth, birth weight, Pre-eclampsia, prematurity, fetal death, and hyperbilirubinemia. Concerning preterm delivery, maternal age, small for gestational age, placental abruption, and (NICU) admission, no statistically significant difference was found between the two groups. There was a statistically significant difference between the two groups regarding birth weight and EGA.***

Conclusion: ***Compared with aspirin, heparin significantly improved live birth, age at delivery during gestation, reduced IUGR occurrence, miscarriage, and pre-eclampsia. There are no significant risks to either the mother or the unborn child when using LMWH during pregnancy to avoid RM in women with APS compared to low-dose aspirin (LDA).***

Keywords: Antiphospholipid syndrome, Pre-eclampsia, Anticoagulants

1. Introduction

At least one kind of circulating antiphospholipid antibody (aPL)[1] indicates antiphospholipid syndrome (APS). This autoimmune disorder may cause thrombotic events in the veins or arteries/or pregnancy morbidity, like antibodies against anticardiolipin (aCL), lupus anticoagulant (LA), and antiβ2-glycoprotein 1 (β2GPI). A patient may show signs of autoantibody subtypes 1, 2, or all three. Every patient must have their antibodies tested.[2,3] "Single positive," "double positive," and "triple positive" are the terms used to describe the amount of positive antibody tests.[4]

Preeclampsia, miscarriage, thromboembolism, premature birth, and perinatal death are among the dangerous pregnancy complications that women with APS are more likely to have.[5,6] Just twenty-five percent of pregnant women with APS who do not receive therapy have a baby who is born healthy. With the advent of low-dose aspirin and LMWH, this number has significantly improved to roughly seventy percent.[1]

Antithrombotic and anti-aggregating medicines are the mainstays of the present therapeutic standard for APS during pregnancy. There is still no consensus on the best way to mix aspirin with heparin, but doing so enhances the live birth rate and decreases treatment failures, which can reach 20-30%.[7] Finding out how anticoagulant medication administration affects the rate of live births. This study's main objective was to examine APS's effects on pregnancy outcomes in women.

Accepted 21 June 2024.
Available online 31 June 2024

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https://doi.org/10.58675/2682-339X.2502

2. Patients and methods

Eighty prospective mothers who tested positive for lupus anticoagulants in the past and anticardiolipin immunoglobulin antibody tests who visited the obstetrics and gynecology department at El Hussein Hospital, one of the Al Azhar University Hospitals between January 2022 and June 2022 were the subjects of this prospective randomized control study. Forty pregnant women diagnosed with APS were divided into two groups at random: (1) those given LMWH and (2) those given aspirin.

Inclusion Criteria: Age 18 – 40, BMI 19 – 30, and positive APS

Exclusion Criteria: Systemic lupus erythematosus patients, women with a thrombotic past, any comorbidity (gastric ulcer, renal, hepatic, neurological, nephrological, DM, endocrine, etc.), age < 18 and > 40 years Patients with a history of or present treatment with heparin, any anticoagulant, corticosteroids, nonsteroidal anti-inflammatory drugs, uterine malformations found through hysterosalpingography, cervical incompetence, luteal phase defect, hyperprolactinemia, polycystic ovarian syndrome, thrombocytopenia (<100,000/ml), bleeding tendencies, multiple gestations, and hyperprolactinemia are also considered.

Sample Size (n):

Serdar et al.,[8] provided the groundwork for our investigation. The following assumptions were considered while calculating the sample size by utilizing Epi Info STATCALC: The study was conducted with a margin of error of five percent and a power of eighty percent, using a two-sided confidence level of 95%. The output from Epi-Info could only be used to retrieve a maximum of 72 samples. Hence, to provide for potential attrition throughout the follow-up period, an increase was made to the sample size to Eighty cases.

$$\left(\frac{Z_{a/2} + Z_B}{P_1 - P_2}\right)^2 (p_1q_1 + p_2q_2)$$

Takazawa& Morita. [9]

n = sample size

Z a/2 (The crucial number that demarcates the center 95% of the Z distribution)

ZB (The crucial number that demarcates the center 20% of the Z distribution)

p1 = prevalence in case group

p2 = prevalence in the control group.

q = 1-p

Methods:

Patients were subjected to Comprehensive patient history collection; physical examination (including a full body, abdomen, and local scans), and diagnostic testing.

Procedure: Eighty women who met the study's inclusion requirements were divided into two groups employing a computer-generated system of random numbers in opaque, sealed envelopes with sequential numbers. A staff nurse divided the ladies into two groups and sequentially gave each group 40 aspirin pills and 40 LMWH pills. The patient began taking prenatal vitamins before conception and maintained taking them throughout the pregnancy. They also took a combination of oral calcium and vitamin D3 supplements (600 mg and 400 IU, once, respectively). Upon a positive serum pregnancy test, anticoagulant medication was initiated immediately. The women in the aspirin group were given eighty-one milligrams of Juspirin daily. In comparison, the women in the LMWH group were given forty milligrams of enoxaparin subcutaneously once a day. At six weeks of gestation, a transvaginal ultrasound by(SAMSUNG (SONOACE) X6, Model 2015, Made in Korea) machine verified the viability of the fetus. Prenatal checkups were conducted weekly at enrollment and continued every two weeks until the mother gave birth. During the first twenty-four weeks of pregnancy, the mother began to have serial ultrasounds every two weeks to track her unborn child's development. Before beginning treatment, pre-treatment platelet counts were taken, followed by two weekly counts for the first two months and, subsequently, 4 weekly counts to identify when thrombocytopenia begins. Heparin medication was stopped when the platelet count dropped below 100,000/milliliters or when there was a fifty percent reduction from the initial platelet count. Up to week thirty-five, patients took 81 milligrams of aspirin daily. To facilitate the closure of the Ductus Arteriosus and to avoid bleeding during childbirth, aspirin was discontinued. To lower the risk of epidural hematoma if the patient needed anesthesia for a cesarean delivery, LMWH was administered up until thirty-seven weeks and then discontinued. The following pregnancy outcomes were recorded: abortion in the first or second trimester, intrauterine growth restriction, premature labor, intrauterine hemorrhage, live birth, gestational ages, and birth weight. The results of the pregnancy were documented. Respiratory distress, hospitalization to the NICU, or hyperbilirubinemia were all considered unfavorable perinatal outcomes.

Ethical Consideration: The Al-Azhar University Institutional Review Board has previously reviewed and approved the study protocol. The Al-Azhar Faculty of Medicine's Ethical Committee also gave its stamp of approval. The study's participants all gave their signed, informed consent. All participants' right to privacy and confidentiality was honored throughout the research.

3. Results

Table 1. Information on the research population's demographics

	LMWH GROUP (N = 40)	ASPIRIN GROUP (N = 40)	TEST OF SIG.	P
MATERNAL AGE (YEARS)	20-37	22-38	t = -1.06	0.292
MEAN ± SD.	28.88 ± 4.15	29.82 ± 3.86		
MEDIAN (IQR)	29(26 - 32.25)	30(27 - 33)		
RANGE (MIN-MAX)	17(20 - 37)	16(22 - 38)		
WEIGHT (KG)	53-87	53-85	t = 0.338	0.736
MEAN ± SD.	72.18 ± 7.7	71.6 ± 7.52		
MEDIAN (IQR)	73.5(66.75 - 78)	72(68 - 77)		
RANGE (MIN-MAX)	34(53 - 87)	32(53 - 85)		
BMI (KG/M2)	19.2-29.2	19.1-27.5	t = 4.371	<0.001
MEAN ± SD.	24.59 ± 2.42	22.42 ± 2		
MEDIAN (IQR)	24.9(23.35 - 26.25)	22.5(21.1 - 23.52)		
RANGE (MIN-MAX)	10(19.2 - 29.2)	8.4(19.1 - 27.5)		

t: Independent T test, SD: standard deviation, IQR: interquartile range, p: p value for comparing between the studied groups, P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.001: Highly significant

Table 1 found a highly significant difference in body mass index (BMI) between the two groups, but no such difference in maternal age or weight.

Table 2. Outcome data among patients who had miscarriage

	LMWH GROUP (N = 40)		ASPIRIN GROUP (N = 40)		TEST OF SIG.	P
	n	%	n	%		
MISCARRIAGES N (%)	4	10%	14	35%	X2 = 7.168	0.007
EGA AT LOSS(WEEKS)	4-17		6-20		t = -2.471	0.016
MEAN ± SD.	10.68 ± 3.29		12.4 ± 2.94			
MEDIAN (IQR)	10.5(8 - 13)		12(10.75 - 14.25)			
RANGE (MIN-MAX)	13(4 - 17)		14(6 - 20)			

x2: Chi- Square test

Table 2 demonstrated that, with relation to miscarriages & EGA at loss, there was a substantial difference between the two research groups.

Table 3. Results for patients who gave birth to living children

	LMWH GROUP (N = 40)		ASPIRIN GROUP (N = 40)		TEST OF SIG.	P
	n	%	n	%		
LIVE BIRTHS N (%)	36	90%	26	65%	X2 = 7.168	0.007
EGA AT BIRTH (WEEKS)	36-42		33-40		t = 5.202	<0.001
MEAN ± SD.	37.92 ± 1.21		36.17 ± 1.75			
MEDIAN (IQR)	38(37 - 39)		36.5(35 - 37)			
RANGE (MIN-MAX)	6(36 - 42)		7(33 - 40)			
BIRTH WEIGHT (GRAMS)	2639-4304		1768-4054		t = 3.475	0.001
MEAN ± SD.	3265.1 ± 363.43		2896.72 ± 563.34			
MEDIAN (IQR)	3262(3030 - 3402.5)		2934.5(2615.5 - 3246.25)			
RANGE (MIN-MAX)	1665(2639 - 4304)		2286(1768 - 4054)			

Table 3 revealed that the two groups of researchers differed significantly with respect to EGA at delivery, as well as with respect to live births & birth weight.

Table 4. Obstetric & maternal problems in live birth patients

	LMWH group (n = 36)		Aspirin group (n = 26)		Test of Sig.	p
	n	%	n	%		
PRE-ECLAMPSIA N (%)	3	8%	10	38%	X2 = 8.269	0.004
PRETERM DELIVERY N (%)	5	14%	5	19%	X2 = 0.318	0.573
IUGR N (%)	4	11%	9	35%	X2 = 5.033	0.025
PREMATURITY N (%)	9	25%	14	54%	X2 = 5.383	0.02

Table 4 found that while preterm delivery was not significantly different between the 2 groups, pre-eclampsia, intrauterine growth restriction, & premature birth was.

Table 5. Complications associated with pregnancy in the study population

	LMWH GROUP (N = 40)		ASPIRIN GROUP (N = 40)		TEST OF SIG.	P
	n	%	n	%		
FETAL DEATH N (%)	4	10%	14	35%	X2 = 7.168	0.007
SMALL FOR GESTATIONAL AGE N (%)	5	13%	10	25%	X2 = 2.051	0.152
PLACENTAL ABRUPTION N (%)	2	5%	5	13%	X2 = 1.409	0.235

Table 5 discovered that while both groups had similar rates of small for gestational age & placental abruption, there were statistically significant variations in the rates of fetal death.

Table 6. outcomes for newborns in the study population

	LMWH GROUP (N = 40)		ASPIRIN GROUP (N = 40)		TEST OF SIG.	P
	n	%	n	%		
ARDS N (%)	3	8%	7	18%	X2 = 1.829	0.176
NEONATAL ICU					X2 =	0.136

N (%)	2	5%	6	15%	2.222	
HYPER-BILIRUBINEMIA					X2 = 4.021	0.045
N (%)	4	10%	11	28%		

Table 6 found that whereas hyperbilirubinemia was significantly different between the two groups, ARDS as well as neonatal intensive care unit admissions were not.

4. Discussion

Upon analyzing our data, we found that the mean maternal age in the LMWH group was 20–37, with a standard deviation of 28.88 ± 4.15, while the mean maternal age in the Aspirin group was 22–38, with a standard deviation of 29.82 ± 3.86. Notably, the two groups had no statistically significant difference (p= 0.292).

Consistent with our results, the study of Alalaf,[10] analyzed the success rate of giving birth in a study that randomly allocated women to receive either low molecular weight heparin (Bemiparin) or low dosage aspirin (LDA) if they experienced recurrent miscarriages during the first trimester due to antiphospholipid antibody syndrome (APS). In all, 141 women participated in the research; sixty- of those women were given low-dose Aspirin (LDA), while 80 were given heparin, a type of low molecular weight heparin. The mean age of the women who received Bemiparin (31.44 ± 5.811) was not significantly different from those who received LDA (30.61 ± 6.325 years). Statistical analysis revealed no significant difference (p=0.736) between both groups in the present investigation. In the Aspirin group, the weight varied between 53 and 85, while in the LMWH group, it ranged from 53 to 87, with an average ± standard deviation of 71.6 ± 7.52. Both the LMWH and Aspirin groups had BMIs ranging from 19.1 to 27.5, with LMWH having a mean standard deviation of 24.5 and Aspirin having a mean standard deviation of 22.4.

This compares with the study of Abdel-Qader et al.,[11] which looked to assess the safety and effectiveness of combining low-molecular-weight heparin and LDA with unfractionated heparin (UFH) and LDA in the treatment of pregnant women experiencing recurrent pregnancy loss due to antiphospholipid syndrome. It found that of the 242 females assigned to the two groups, the BMI (kilogram /m2) of the LMWH group was 25.84±2.75, and that of the UFH group was 25.23±2.91.

Regarding the current study's conclusion, the miscarriage rate differed significantly (p=0.007) between the two analyzed groups. The EGA at a loss in the Aspirin group varied from six to twenty with a mean, standard deviation = 12.4 ± 2.94, while there was a statistically significant difference (p=0.016) between the two groups. In the LMWH group, the EGA at loss ranged from four to seventeen with mean ± standard deviation = 10.68 ± 3.29.

We can be supported by Hamulyák et al.,[12] who found that taking Aspirin alone may not be as effective at preventing pregnancy loss as taking heparin with Aspirin (RR 0.48, ninety-five percent confidence interval 0.32, 0.71; 1295 female; 5 studies; low-certainty evidence).

In addition to the previously mentioned results, we also discovered that the number of live births varied significantly (p=0.007) between the two groups under study. The EGA varied from 36 to 42 in the LMWH group at birth, with a mean ± standard deviation of 37.92 ± 1.21, while the EGA ranged from 33 to 40 in the Aspirin group, with a mean ± standard deviation of 36.17 ± 1.75. There was a highly significant difference (p= <.001) between both groups.

We can find evidence from Hamulyák et al.,[12] whereby a random meta-analysis was conducted for the primary outcome of live birth, incorporating five trials (1295 women) that compared heparin (UFH or LMWH) in combination with Aspirin to Aspirin alone. When compared to Aspirin alone, heparin plus Aspirin may result in more live births (RR 1.27; ninety-five percent confidence interval 1.09 to 1.49; Chi2 = 7.71, Tau2 = 0.01; df = 4 (P = 0.10); I2 = 48 percent).

In contrast, birth weight in the Aspirin group ranged from 1768 to 4054 with a mean standard deviation = 2896.72 ± 563.34. There was a statistically significant difference (p=0.001) between 2 groups. In the current study, birth weight in the LMWH group ranged from 2639 to 4304 with mean ± standard deviation = 3265.1 ± 363.43.

Consistent with our results, Alalaf[10] reported that the mean fetal weight in kilograms in the LDA and LMWH groups was 2.323 ± 1.50 and 3.129 ± 1.263, respectively, with a statistically significant difference (p-value = 0.001) between both groups.

The results above showed a significant difference (p-value = 0.004) in pre-eclampsia between the two study groups but not a statistically significant difference (p = 0.573) in preterm delivery. Furthermore, there was a significant difference (p-value =0.025) in IUGR between the two groups under study. There was a significant difference (p-value =0.02) in the two study groups' levels of prematurity.

Consistent with our results, Hamulyák et al.,[12] reported that three out of thirty-seven women in the low molecular weight heparin with Aspirin treated group, one out of thirty-three women in the UFH + Aspirin treated group experienced pre-eclampsia (RR 2.09, ninety-five percent confidence interval (CI) 0.33 to 13.22). A modest

percentage of cases and rates—2/30 & 3/20 in the groups treated with a more significant dose of heparin (UFH or low molecular weight heparin) and 1/30 & 0/19 in the groups treated with a lower dose of heparin—were reported to have IUGR, with no discernible difference between interventions. It is interesting to note that there was a significant difference (p = 0.007) between the two study groups in the current study regarding fetal death. There was no statistically significant difference between the two study groups regarding Small gestational age (p= 0.152). There was no statistically significant difference (p-value = 0.235) in placental abruption between the two groups under study.

Regarding the other pregnancy problems, results from Askie & Duley's[13] meta-analyses have demonstrated a significant decrease in the number of women receiving antiplatelet drugs (mainly Aspirin) who were at high risk for pre-eclampsia. Pregnancies that progressed beyond 20 weeks of gestation showed benign maternal and fetal-neonatal outcomes in all clinical trials; the incidences of fetal death, pre-eclampsia, severe placental insufficiency, as well as iatrogenic preterm birth were comparable to those of the general obstetric population.

Outcomes for newborns in the population under study. There was no statistically significant difference (p=0.176) in ARDS between the two groups under study. There was no statistically significant difference (p=0.136) between the two study groups about the Neonatal ICU. There was a significant difference (p=0.045) in hyperbilirubinemia between the two groups under study. Mazarico et al.,[14] stated that no significant differences were observed in Apgar scores, newborn hospitalization, neonatal death, or composite unfavorable neonatal morbidity between women treated with heparin controls, consistent with our findings.

4. Conclusion

Compared to Aspirin, we concluded that heparin significantly decreased the occurrence of intrauterine growth restriction (IUGR), miscarriage, and pre-eclampsia while significantly increasing live birth and gestational age at birth. To prevent RM in women with APS, LMWH is an alternative to low-dose Aspirin (LDA) during pregnancy. It is a safe and effective medication with a high rate of live births and no significant issues for the mother or the unborn child.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

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